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Diet and nutrition as risk factors for multiple myeloma among blacks and whites in the United States

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Abstract

Objectives: To explore whether dietary factors contribute to the risk of multiple myeloma and the two-fold higher incidence among blacks compared to whites in the United States.
Methods: Data from a food-frequency questionnaire were analyzed for 346 white and 193 black subjects with multiple myeloma, and 1086 white and 903 black controls who participated in a population-based case–control study of multiple myeloma in three areas of the United States.
Results: Elevated risks were associated with obese *vs*. normal weight (OR = 1.9, 95% confidence interval (CI) = 1.2–3.1 for whites and OR = 1.5, 95% CI = 0.9–2.4 for blacks), while the frequency of obesity was greater for black than white controls. Reduced risks were related to frequent intake of cruciferous vegetables (OR = 0.7, 95% CI = 0.6–0.99) and fish (OR = 0.7, 95% CI = 0.5–0.9) in both races combined, and to vitamin C supplements in whites (OR = 0.6, 95% CI = 0.5–0.9) and blacks (OR = 0.8, 95% CI = 0.5–1.4), with the frequency of vitamin supplement use being greater for white than black controls. However, frequent intake of vitamin C from food and supplements combined was associated with a protective effect in whites (OR = 0.6, 95% CI = 0.4–0.9), but not blacks (OR = 1.2, 95% CI = 0.8–2.1).
Conclusions: The greater use of vitamin C supplements by whites and the higher frequency of obesity among blacks may explain part of the higher incidence of multiple myeloma among blacks compared to whites in the United States. In addition, the increasing prevalence of obesity may have contributed to the upward trend in the incidence of multiple myeloma during recent decades.

Introduction

Multiple myeloma is a B-cell malignancy that is expected to account for over 11,000 deaths in the United States during 2000 [1]. For the period 1992–1996, the age-adjusted incidence rate was 4.1/100,000 for whites and 9.5/100,000 for blacks [2]. Although the incidence of multiple myeloma in the United States has increased 14% over the time period 1973–1996 [2], little is known about its etiology. To investigate risk factors for this cancer and reasons for the 2.3-fold higher incidence among blacks, we conducted a population-based case–

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control study among blacks and whites in three geographic regions of the United States. In this paper, we examine the role of dietary and nutritional factors in the risk of multiple myeloma, and its possible effect on the black/white differential in incidence in the United States. A few studies have investigated the relationship between selected dietary items and obesity in the development of multiple myeloma [3–6]. To our knowledge, this is the first population-based case–control study to comprehensively evaluate the role of dietary and nutritional factors in the etiology of multiple myeloma and its contribution to the excess incidence in blacks compared to whites.

Materials and methods

This population-based case–control study of multiple myeloma, conducted during 1986 to 1989, was one component of a multi-center study of four types of cancer (multiple myeloma, esophagus, pancreas, and prostate) that occur more frequently among blacks than whites. For efficiency, one large general-population control group was used for all four cancer types. Subjects were residents of geographic areas covered by three population-based cancer registries: the Georgia Center for Cancer Statistics (DeKalb and Fulton counties), the Metropolitan Detroit Cancer Surveillance System (Macomb, Oakland, and Wayne counties), and the New Jersey State Cancer Registry (10 counties).

Eligible cases were all white and black residents aged 30–79 newly diagnosed with multiple myeloma (as reported on pathology, hematology, outpatient, or tumor registry records at hospitals in the three areas) between 1 August 1986 and 30 April 1989. Of the 581 white and 309 black cases of multiple myeloma ascertained, interviews were conducted with 367 whites (63%) and 208 blacks (67%). Non-response was due to death (21% for both races), illness (whites 7%, blacks 6%), or refusal to be interviewed (whites 8%, blacks 5%).

Controls were frequency-matched to the age, race, gender, and area distribution of cases with all four types of cancer combined. For each geographic area, registry data from prior years were used to estimate the race-, gender-, and age-specific (5-year age groups) numbers of cases expected to construct a sampling frame for controls. Controls were selected from two sources. Random-digit dialing (RDD) techniques were used to select controls aged 30–64 [7]. Computerized listings of Medicare recipients provided by the Health Care Financing Administration (HCFA) stratified by age, gender, and race were used to select systematically (after a random start) controls aged 65–79.

In-person interviews were conducted with the cases and controls by trained interviewers, usually in the subject's home. Informed consent to participate in the study was obtained from each subject prior to interview. Detailed information was obtained on several factors possibly related to multiple myeloma, including usual adult diet, use of alcohol and tobacco, lifetime occupation, medical history, family history of cancer, and sociodemographic factors. Among controls, interviews were conducted with 1227 (78% of both whites and blacks) of the 1568 eligible subjects from RDD and 926 (75%) of the 1232 persons selected from HCFA files. The interview response rates for the HCFA controls were 73% for whites and 78% for blacks. Since the response rate for the household screening phase for the RDD controls was 86%, the overall participation rate for RDD controls was 67%. Among eligible controls, refusal to be interviewed was the most common reason for non-response (whites 17%, blacks 13%), followed by illness or death (whites 3%, blacks 4%), and other problems (whites 3%, blacks 4%). Excluded from all analyses were 15 white male controls aged 30–34 years because there were no comparably aged white male cases. Further details of case/control selection have been published elsewhere [8].

Dietary analyses were based on the 346 white cases (183 male, 163 female; 94% of eligibles), 193 black cases (87 male, 106 female; 94% of eligibles), 1086 white controls (678 male, 408 female; 93% of eligibles), and 903 black controls (561 male, 342 female; 93% of eligibles) who answered at least 95% of the individual food items in the questionnaire. A detailed description of the dietary assessment methodology is provided elsewhere [9]. Briefly, subjects were asked to recall their usual frequency, excluding the past five years, (*i.e.* "How often did you usually have (TYPE) before five years ago?") of consumption of 60 specific food items (*e.g.* bananas, broccoli, beef) or groups of similar food items (*e.g.* bread, rolls, or biscuits). Responses were reported and recorded in number of times per day, week, month, or year. Although there was no independent validation of our food-frequency questionnaire, it was patterned after a dietary instrument developed by Block *et al.* [10] that has been shown to yield generally reliable information on food intake. To evaluate dietary factors, individual foods were categorized into food groups as outlined in the Appendix. Nutrient intakes were estimated based on the frequency of consumption of each food item and the nutrient content of an average serving for males and females obtained from the National Health and Nutrition Examination Survey (NHANES II) nutrient database [11, 12]. Estimates for starch and sugar were obtained from *McCance and Widdowson*'s,

and USDA, respectively [13, 14]. Four consumption categories ranging from low to high were created for each food group and selected nutrients by dividing the frequency distribution for the controls into approximate quartiles. Subjects were also asked about their use of vitamin supplements five years before the interview, including the number of times used per week and the duration of use. To compute amount of vitamin C from diet plus supplements, supplement dose was estimated as 60 mg from a multivitamin and 250 mg from a separate vitamin C supplement. Body mass index (BMI, kg/m^2) was determined from reported usual adult weight and height. The BMI continuous variable was used to make two categorical variables. One based on the National Institutes of Health guidelines [15]: <18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight), and ≥30 (obese). The other (used as a covariate in the analysis of diet) was based on quartiles of the control distribution (<22.5, 22.5–24.5, 24.6–27.1, ≥27.2).

Data were analyzed using unconditional logistic regression [16]. Odds ratios (OR) and 95% confidence intervals (CI) were obtained using the BMDPLR procedure [17]. All race-specific models for the food group and nutrient analyses included the variables of age at diagnosis/interview (<65, ≥65), geographic area (Atlanta, Detroit, New Jersey), gender (male, female), body mass index (in quartiles) and calories from food, in quartiles, for energy adjustment (<1214, 1214–1557, 1558–1988, ≥1989). Nutrient density models (nutrient per thousand calories) were used for energy adjustment to evaluate the macro- and micro-nutrients. Addition of education as a potential confounder did not substantially alter the ORs; thus, it was not included in the final logistic models. To test for linear trend, categorical variables were entered as continuous variables in the logistic models, with each level represented by the median value of that category in the control group. Both races combined, as well as gender-specific and race-gender-specific results, will be presented in the text where appropriate.

Results

BMI, caloric intake, and number of meals per day

Table 1 presents the adjusted ORs among whites and blacks for BMI, caloric intake, and meals per day. Compared to subjects of normal weight, elevated risks of multiple myeloma were seen in both races for BMI defined as overweight (OR = 1.5 for whites, OR = 1.3 for blacks) or as obese (OR = 1.9 for whites, OR = 1.5

Table 1. ORs for multiple myeloma in whites and blacks according to selected nutritional variables[a]

	Whites				Blacks			
	Case	Control	OR[b,c]	95% CI	Case	Control	OR[b,c]	95% CI
Body mass index[d,e]								
Underweight	3	15	0.6	0.2–2.3	3	12	1.1	0.3–4.2
Normal	159	597	1.0	–	73	414	1.0	–
Overweight	148	404	1.5	1.1–2.0	79	355	1.3	0.9–1.8
Obese	35	66	1.9[f]	1.2–3.1	36	118	1.5	0.9–2.4
Calories from food[g]								
<1214	74	256	1.0	–	50	238	1.0	–
1214–1557	95	273	1.5	1.0–2.2	45	220	1.2	0.7–1.8
1558–1988	99	289	1.5	1.0–2.1	51	205	1.5	0.9–2.3
>1988	76	259	1.4	0.9–2.1	45	236	1.3	0.8–2.2
Number of meals eaten per day[h]								
1	10	39	1.0	–	8	66	1.0	–
2	85	323	1.0	0.5–2.2	89	411	1.8	0.8–3.9
≥3	249	715	1.3	0.6–2.7	94	421	1.7	0.8–3.7

[a] Excludes subjects with missing values.
[b] All risks relative to 1.0 for those in the lowest category.
[c] Adjusted for age, area, and gender.
[d] Underweight (BMI < 18.5), normal (BMI 18.5–24.9), overweight (BMI 25.0–29.9), obese (BMI ≥ 30).
[e] Also adjusted for food calories.
[f] p for trend <0.001.
[g] Also adjusted for BMI in quartiles.
[h] Also adjusted for food calories and BMI in quartiles.

for blacks). A significant trend in risk with increasing BMI, excluding the underweight category, was seen for white men and women (p for trend < 0.001), and for black women (p for trend $= 0.042$) but not black men [for whom risks for being overweight (OR = 1.1) or obese (OR = 1.0) were not elevated]. Using BMI in quartiles yielded similar results. Among controls, a greater percentage of black men (9.6%) and black women (18.9%) were obese compared to white men (6.5%) and white women (5.4%). Although no significant dose–response gradients were noted, elevated risks were associated with intake of 1214 or more calories from food per day for blacks and whites. Significant associations were not observed for the number of meals eaten per day, although ORs were nonsignificantly elevated for whites (OR = 1.3) with three or more meals and blacks (OR = 1.8) with two or more meals compared to those with only one. Independent effects of BMI and total caloric intake were noted when evaluated jointly.

Food groups

Adjusted ORs for selected foods and food groups are presented in Table 2. No significant associations were observed for dairy products, bread/grains/cereal, red meat, processed meat, poultry, or desserts. In addition, no food or food group showed a significant trend in risk with either increasing or decreasing consumption for whites and blacks. However, a significant negative dose gradient for fish consumption was observed among blacks (p for trend $= 0.043$) and among blacks and whites combined (p for trend $= 0.012$). The combined ORs for low, medium, and high tertiles of fish consumption were 1.0, 0.8 (95% CI = 0.6–1.0), and 0.7 (95% CI = 0.5–0.9). For both races, there was a slight protective effect of higher consumption of some vegetables (with the exception of legumes in blacks). A reduced risk was associated with frequent consumption of cruciferous vegetables among white men and women, and among black women but not black men (data not shown); a greater percentage of black (31%) than white (19%) controls were in the highest intake category (greater than four servings per week). There was a significant trend of decreased risk with increased intake of cruciferous vegetables for blacks and whites combined (p for trend $= 0.045$). The ORs for the lowest to the highest intake quartile were 1.0, 0.9 (95% CI = 0.7–1.1), 0.8 (95% CI = 0.6–1.0) and 0.7 (95% CI = 0.6–0.99). However, there were no significant trends in risk for the lowest to the highest intake quartile of vitamin C-rich vegetables, other than cruciferous vegetables among whites (OR = 1.0, 1.0, 0.9, 0.9; p for trend = 0.646) or blacks (OR = 1.0, 1.1, 0.9, 1.0; p for trend = 0.979) (data not shown).

Table 2. ORs for multiple myeloma in whites and blacks according to consumption level of selected foods and food groups[a]

Food group	Quartiles of consumption							
	Whites				Blacks			
	Low 1	2	3	High 4	Low 1	2	3	High 4
Dairy products	1.0	1.1	0.8	0.9	1.0	1.6	1.0	1.1
Eggs	1.0	1.2	1.7[c]	1.5	1.0	1.1	1.6	1.4
Breads, grains, and cereal	1.0	1.0	1.2	1.1	1.0	1.1	1.1	0.9
Meat, poultry, and fish	1.0	0.8	0.8	0.7	1.0	1.5	1.0	1.3
Red meat	1.0	0.8	0.8	0.8	1.0	1.4	1.4	1.3
Processed meat	1.0	0.9	0.9	0.7	1.0	1.1	1.1	1.0
Poultry	1.0	0.7	0.9	0.9	1.0	1.5	1.0	1.1
Fish[b]	1.0	0.8		0.8	1.0	0.8		0.6[c,d]
Fruits	1.0	1.1	1.4	1.0	1.0	1.3	1.7[c]	1.2
Citrus	1.0	1.2	1.4	1.3	1.0	1.5	1.4	1.6
Noncitrus	1.0	1.3	1.2	1.3	1.0	1.0	1.3	0.9
Vitamin A-rich	1.0	1.1	1.1	1.2	1.0	1.0	1.0	1.0
Vegetables	1.0	0.8	0.9	0.7	1.0	0.9	0.6[c]	0.9
Cruciferous	1.0	0.8	0.9	0.7[c,d]	1.0	1.0	0.7	0.9
Dark green	1.0	0.8	0.9	0.7	1.0	0.8	0.7	0.8
Dark yellow	1.0	1.1	1.0	0.9	1.0	1.0	1.1	1.0
Legumes	1.0	0.9	0.9	0.8	1.0	1.7[c]	1.6	1.2
Vitamin A-rich	1.0	0.9	1.0	0.7	1.0	1.0	1.1	0.9
Fruits and vegetables	1.0	1.2	1.0	0.9	1.0	1.0	0.9	0.9
Juice	1.0	0.8	1.1	1.0	1.0	1.2	1.7[c]	1.5[d]
Vitamin A-rich	1.0	1.1	1.1	0.9	1.0	1.0	0.9	0.7
Dessert	1.0	1.1	0.9	1.0	1.0	1.6	1.2	1.2

[a] ORs adjusted for age at diagnosis/interview, study area, gender, calories from food, and BMI in quartiles.
[b] ORs calculated for tertiles of consumption.
[c] $p < 0.05$.
[d] p for trend < 0.05.

In general, for both races, there was a slight elevation in risk for higher consumption of fruit, especially citrus fruit. For both races combined, the ORs for the lowest to the highest quartile of citrus fruit consumption were 1.0, 1.3 (95% CI = 1.0–1.8), 1.4 (95% CI = 1.1–2.0), and 1.4 (95% CI = 1.0–1.9) (p for trend $= 0.144$). There was also a positive trend of increasing risk with increasing consumption of eggs that was evident for men (p for trend $= 0.008$), but not women. The ORs for the lowest (one or fewer eggs per week) to the highest (greater than four eggs per week) quartile of egg intake for men were 1.0, 1.4 (95% CI = 0.9–2.2), 2.3 (95% CI = 1.5–3.5), and 2.1 (95% CI = 1.4–3.6). Among blacks, there was a significant trend of increased risk with increased intake of fruit or vegetable juice (p for

trend = 0.031). The ORs for blacks in the highest quartile (*i.e.* greater than 1.03 servings per week) and second-highest quartile (approximately one serving per week) *vs.* the lowest quartile (*i.e.* less than one serving per month) was 1.5 (95% CI = 0.9–2.4) and 1.7 (95% CI = 1.05–2.8), respectively. There was no increase in risk associated with intake of juice for whites. Orange juice is the major contributor to this food group.

Nutrients

Table 3 shows adjusted ORs by race for consumption of specific nutrients and other dietary constituents. No significant associations were observed for starch, sugar, fiber, total protein, vitamin C from vegetables, vitamin A including carotenoids, the B vitamins, calcium, or iron. For both races combined, there was a slight nonsignificant elevation in risk for higher consumption of starch and sugar, a slight nonsignificant protective effect for higher consumption of fiber, and a significant protective effect for frequent intake of fat. The ORs for the lowest to the highest intake of total fat were 1.0, 1.0 (95% CI 0.7–1.3), 0.9 (95% CI 0.7–1.2), and 0.7 (95% CI 0.5–0.9), respectively (p for trend = 0.020). Protective effects of plant fat were evident in both blacks and whites, while risks for heavy intake of animal fat were elevated in blacks but not whites. There was also a significant trend of increasing risk with increasing intake of cholesterol that was evident for white (p for trend = 0.007) and black (p for trend = 0.020) men, but not women. The ORs for the lowest to the highest quartile of cholesterol intake for white and black men combined were 1.0, 1.5 (95% CI = 0.9–2.5), 2.2 (95% CI = 1.3–3.5), and 2.2 (95% CI = 1.4–3.6) (p for trend <0.001). Among blacks, but not whites, there was a significant positive gradient in risk with consumption of vitamin C from fruit and fruit juice (p for trend = 0.015); the OR for the highest *vs.* the lowest quartile of consumption was 1.8 (95% CI = 1.1–3.0). The risk for high intake of vitamin C from fruit and fruit juice was greater for black women (OR = 2.2, 95% CI = 1.03–4.7) (p for trend = 0.029) than black men (OR = 1.5, 95% CI = 0.7–3.1) (p for trend = 0.229).

Table 3. ORs for multiple myeloma in whites and blacks according to intake of specific nutrients and dietary constituents[a]

Nutrient	Quartiles of consumption							
	Whites				Blacks			
	Low 1	2	3	High 4	Low 1	2	3	High 4
Total carbohydrates	1.0	1.1	1.1	1.3	1.0	1.1	1.3	1.4
Starch (Britain)	1.0	1.1	1.1	1.3	1.0	1.1	1.1	1.4
Simple sugar (US)	1.0	1.0	1.2	1.2	1.0	1.5	1.7	1.5
Fiber	1.0	0.7	1.0	0.8	1.0	1.3	1.0	0.8
Total fat	1.0	1.0	1.0	0.7[b]	1.0	0.9	0.7	0.8
From plants	1.0	0.7	0.8	0.7	1.0	0.6	0.8	0.8
From animals	1.0	0.9	0.9	0.8	1.0	1.3	1.5	1.1
Cholesterol	1.0	1.2	1.5[b]	1.3	1.0	1.0	1.2	1.4
Total protein	1.0	1.0	0.9	1.0	1.0	0.9	1.3	0.8
Vitamin C	1.0	0.9	0.9	1.1	1.0	1.4	1.7[b]	1.4
From fruit and juice	1.0	1.0	1.0	1.2	1.0	1.4	1.6	1.8[b,c]
From vegetables	1.0	0.8	0.9	1.0	1.0	0.7	0.8	0.8
Vitamin A	1.0	1.2	1.2	0.8	1.0	1.0	1.1	1.0
β-Carotene	1.0	1.2	1.1	0.8	1.0	1.0	1.2	0.9
Retinol	1.0	1.2	1.0	1.1	1.0	0.9	1.2	1.2
B vitamins								
Folate	1.0	0.9	0.8	1.0	1.0	1.0	1.4	1.2
Thiamine	1.0	0.9	0.9	0.9	1.0	0.9	0.8	0.8
Riboflavin	1.0	0.8	0.9	1.1	1.0	0.7	0.7	0.9
Niacin	1.0	1.0	0.9	0.9	1.0	1.1	1.1	0.7
Calcium	1.0	0.6[b]	1.0	0.9	1.0	0.8	0.7	0.9
Iron	1.0	1.2	0.7	1.0	1.0	1.5	1.5	1.0

[a] ORs adjusted for age at diagnosis/interview, study area, gender, calories from food, and BMI in quartiles using the nutrient density method.
[b] $p < 0.05$.
[c] p for trend <0.05.

Vitamin supplements

The proportion of vitamin supplement users was slightly higher for white controls (43%) than black controls (39%), but vitamin C supplement use was substantially higher in whites (20%) compared to blacks (12%) (Table 4). Use of any vitamin supplement was associated with a reduced risk in whites (OR = 0.7) and blacks (OR = 0.8). A significantly reduced risk was observed for use of vitamin C supplements by whites (OR = 0.6, 95% CI = 0.5–0.9), whereas blacks showed a nonsignificant reduction in risk (OR = 0.8, 95% CI = 0.5–1.4). These reductions were seen for each of the four race–gender groups. When the joint effects of BMI (<25, ≥ 25) and vitamin C supplements (yes, no) were assessed, independent effects for each variable were observed. In addition, a significant negative gradient in risk with the number of years of vitamin C supplement use was observed for whites (p for trend <0.05), but not blacks. Vitamin supplement use was categorized into four distinct groups (took neither vitamin C supplements nor multivitamins [referent]; took vitamin C supplements, but not multivitamins; took multivitamins, but not vitamin C supplements; and took both multivitamins and vitamin C supplements). The lowest OR for whites was for those who took vitamin C supplements, but not multivitamins (OR = 0.6, 95% CI = 0.3–1.1), whereas for blacks the lowest risk was for those who took both multivitamins and vitamin C supplements

Table 4. ORs for multiple myeloma in whites and blacks according to use of vitamin supplements[a]

	Whites				Blacks			
	Case	Control	OR	95% CI	Case	Control	OR	95% CI
Ever used vitamins[b,c]								
Never vitamins	226	615	1.0	–	123	552	1.0	–
Ever vitamins	119	465	0.7	0.6–1.0	69	348	0.8	0.6–1.2
Multivitamins	97	376	0.7	0.6–1.0	57	263	0.9	0.6–1.3
Took for <10 years	41	150	0.9	0.6–1.3	30	141	1.0	0.6–1.5
Took for ≥10 years	55	221	0.7	0.5–1.0	27	119	0.9	0.6–1.4
Vitamin A	11	38	0.8	0.4–1.6	7	28	1.1	0.5–2.7
Vitamin B	32	112	0.9	0.6–1.4	17	69	1.0	0.6–1.8
Vitamin C	47	219	0.6	0.5–0.9	22	107	0.8	0.5–1.4
Took for <5 years	16	63	0.9	0.5–1.6	8	44	0.8	0.4–1.8
Took for ≥5 years	30	155	0.6[e]	0.4–0.9	13	63	0.8	0.4–1.5
Cod liver oil	7	29	0.7	0.3–1.8	14	80	0.8	0.4–1.4
Milligrams of vitamin C from food and supplements[d,e,f]								
<110.8	91	258	1.0	–	38	236	1.0	–
110.8–168.3	82	289	0.7	0.5–1.0	46	207	1.2	0.7–1.9
168.4–259.5	102	252	1.0	0.7–1.4	54	241	1.2	0.7–1.9
≥259.6	69	278	0.6[e]	0.4–0.9	53	215	1.2	0.8–2.1

[a] Excludes subjects with missing values.
[b] All risks relative to 1.0 for those who took no vitamins.
[c] Adjusted for age, area, and gender.
[d] All risks relative to 1.0 for those consuming <110.8 mg of vitamin C.
[e] Adjusted for age at diagnosis/interview, study area, gender, food calories, and BMI in quartiles.
[f] p for trend <0.05.

(OR = 0.8, 95% CI = 0.4–1.5) (data not shown). A variable combining intake of vitamin C from supplements and dietary sources yielded inconsistent results for whites and blacks (Table 4). There was a significant negative gradient in risk for whites (p for trend = 0.024), but not blacks. For whites, there was also a significantly reduced risk for the highest compared to the lowest quartile of vitamin C consumption (OR = 0.6), whereas for blacks the risk in the highest category was slightly elevated (OR = 1.2).

Discussion

Our population-based case–control study comprehensively evaluated the risks of multiple myeloma among US whites and blacks in relation to dietary and nutritional factors. We found an elevated risk of multiple myeloma associated with being overweight and obese for both whites and blacks. Reduced risks were associated with frequent intake of vegetables (notably cruciferous vegetables), fish, and vitamin supplements (especially vitamin C).

The elevated risk we observed with overweight and obesity is consistent with the relationship reported by Friedman and Herrinton between obesity and multiple myeloma in two cohorts of outpatients from a health maintenance organization in northern California [3]. In their multiphasic-checkup cohort, there was a significant trend of increased risk with increasing BMI for white men but not the other three race–gender groups [3], whereas our study found elevated risks for above-normal BMI (25 or greater) for all race–gender groups with the exception of black males. In agreement with their northern California pharmacy cohort study [3], we found a stronger effect of BMI in women than in men. The higher prevalence of obesity noted among black than white female controls in our study population is consistent with national survey data [18], and may explain part of the excess incidence of multiple myeloma in black *vs.* white women. The mechanism linking high BMI to multiple myeloma is unclear, but some studies suggest that excess caloric intake and obesity may affect immunologic responses that are involved in the development of this malignancy [19, 20].

The protective effect we observed with cruciferous vegetables has not been previously reported, although an Italian study of multiple myeloma reported an inverse relation with intake of green vegetables [6]. Cruciferous vegetables contain various compounds, including isothiocyanates, dithiothiones, glucobrassicin, and indoles, which have been shown to inhibit the

development of cancer in laboratory animals [19, 21, 22]. They also contain vitamin C, an antioxidant that reduces the endogenous formation of oxygen-free radicals [21, 23].

In experimental studies, vitamin C modulates the *in-vitro* growth of human and mouse myeloma progenitor-stem cells and is a potent inhibitor of T-cell death in mice [24]. These studies suggest that vitamin C may enhance immune responsiveness by preventing damage to the immune cells themselves [25]. In our study, a reduced risk was associated with intake of cruciferous vegetables, which are rich in vitamin C, and with use of vitamin C supplements, which were consumed more often by whites than blacks. While this may partly contribute to racial differences in the incidence of multiple myeloma, it is possible that use of vitamin supplements, particularly vitamin C, is associated with aspects of low-risk lifestyle factors (*e.g.* access to medical care, adequate housing, lower levels of stress) that we did not measure in this study. Anomalous findings were the lack of an association with intake of non-cruciferous vitamin C-rich vegetables, and the positive relation with vitamin C derived from food (especially fruit and fruit juice) seen only in blacks.

A northern Italian study reported that high intake of whole-grain foods (mainly bread) reduces the risk of various cancers including multiple myeloma [4]. Our study found no association with consumption of bread, grains, and cereal, primarily from refined grains.

Our finding of a protective effect of fish intake is consistent with results of an Italian study [5]. It is noteworthy that fish and fish oils contain the polyunsaturated omega-3 essential fatty acids (EFA), eicosapentaenoic and docosahexaenoic acids [26]. Although the mechanisms are unclear [27], there is some evidence that omega-3 EFA may affect cancer development in animals and humans [28, 29]. In experimental studies, omega-3 EFA limited cell growth of a mouse myeloma cell line *in vitro* [30], and fish oil administered to animals and humans suppressed proliferation of both T- and B-cell lymphocytes and enhanced apoptosis [29, 31, 32]. Fish oil also reduces production of the cytokine interleukin 6 [31, 33], a promoter of B-cell differentiation and myeloma cell growth [34, 35].

The positive association we observed between multiple myeloma and cholesterol intake in men most likely reflects the elevated risks among frequent consumers of eggs. In our study, the contribution of eggs to total cholesterol was 51% for white cases and 57% for black cases. We also noted a protective effect of heavy fat intake. Although the main contributors to the fat variable were butter/margarine, milk, eggs, meat, and (females only) mayonnaise, intake of these foods did not vary between cases and controls. Butter/margarine contributed on average about 12% of the fat, but we could not separate the effects of butter from margarine because of the way the questionnaire was worded. Elevated risks associated with animal sources of fat, primarily liver and butter, were reported in an Italian case–control study [6], whereas our study reported increased risks for animal fat in blacks but not whites.

The strengths of our study included the use of a large population-based incident series of blacks and whites newly diagnosed with multiple myeloma, in-person interviews conducted directly with all study subjects generally within 6 months of diagnosis, and exclusion of all respondents judged to be unreliable, thus enhancing the accuracy of risk estimates. There were, however, several limitations of our study, including the potential problem of misclassification in reporting usual dietary intake (most likely non-differential with respect to case/control status), possible biases resulting from relatively low response rates, plus an effect of multiple comparisons and the resulting play of chance that may explain inconsistent associations between whites and blacks.

In summary, our population-based case–control study among blacks and whites in the United States suggests that obesity (as measured by BMI) increases the risk of multiple myeloma, while intake of fish, cruciferous vegetables, and vitamin C supplements may decrease the risk. According to data from the National Health and Nutrition Surveys, the prevalence of overweight US adults (defined as BMI value ≥27.8 for men and ≥27.3 for women) has increased by approximately 30% during the time period 1976–1991 [18]. Thus, if obesity is causally related to multiple myeloma, it may explain part of the upward trend and racial disparity in incidence rates, especially among women. Further, if the relation is causal, the greater use of vitamin C supplements by whites may explain a small portion of the higher incidence of multiple myeloma among blacks.

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Appendix: Individual foods included in each food group

Dairy products: cheese, milk, ice cream.
Bread, grains, and cereal: bread, rolls, or biscuits; cold cereal; hot cereal; rice; spaghetti, macaroni, or noodles.
Meat, poultry, and fish: bacon or sausage; chicken; beef; fish; liver, liverwurst or chopped liver; lunch meats; mixed dish with meat (*e.g.* chili, pork and beans, spaghetti and meat balls); other pork or ham; stew.
Red meat: excludes chicken and fish from "Meat, poultry, and fish" list.
Processed meats: bacon or sausage, lunch meat, hot dogs, other pork or ham.
Fruits: apples or pears, apricots, bananas, cantaloupe, grapefruit, oranges or tangerines, orange or grapefruit juice, fresh peaches or nectarines, canned peaches, watermelon.
Citrus fruits: grapefruit, oranges or tangerines.
Noncitrus fruits: excludes grapefruit, oranges or tangerines, and orange or grapefruit juice from "Fruits" list.
Vitamin A-rich fruits: apricots, cantaloupe, watermelon.
Vegetables: green string beans or lima beans, red beets, broccoli, cooked cabbage, coleslaw, carrots, cauliflower, southern greens (collards, mustard greens, kale), okra, green peas, black-eyed peas or cow peas, white potatoes, sweet potatoes or yams, raw tomatoes, cooked tomatoes, tomato or V-8 juice, tossed salad, spinach, vegetable soup, mixed vegetables, zucchini or yellow squash.
Cruciferous/vitamin C-rich vegetables: broccoli, cooked cabbage, coleslaw, cauliflower, southern greens.
Dark green vegetables: broccoli, southern greens, spinach.
Dark yellow vegetables: carrots, mixed vegetables with carrots, sweet potatoes or yams.
Legumes: green peas, black-eyed peas or cow peas, green string beans or lima beans.
Fruits and vegetables: All items listed under "Fruits" and "Vegetables".
Fruit and vegetable juice: fresh or frozen orange or grapefruit juice, tomato or V-8 juice; vitamin-C fortified fruit drinks.
Vitamin A-rich fruits and vegetables: apricots; cantaloupe; watermelon, carrots; mixed vegetables with carrots; sweet potatoes or yams, broccoli, southern greens, spinach.
Dessert: cake, pie, or cookies; doughnuts; ice cream.

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